UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,364	12/14/2006	Larry I. Benowitz	701039-054385	1709

7590 11/30/2009

David S Resnick
Nixon Peabody
100 Summer Street
Boston, MA 02110-2131

EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
11/30/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,364	BENOWITZ ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above claim(s) *5,6,8-27,33,34,36-55 and 59-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,28-32,35 and 56-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/05/06, 03/14/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' elections without traverse of Group IX, claims 1-9, 28-37, 56-58 drawn to methods wherein the NgR antagonist is a clostridium botulinum C3 ADP-ribosyltransferase encoded by DNA and of the species of CNTF in the reply filed on 11 June 2009 are acknowledged.

Claims 5, 6, 8-27, 33, 34, 36-55 and 59-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11 June 2009.

Claims 1-4, 7, 28-32, 35 and 56-58 are under examination in the instant office action.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 05 September 2006 and 14 March 2008 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Claim Objections

Claims 29, 30, 57 and 58 are objected to because of the following informalities: the claims depend from non-elected base claims, i.e. claim 29 depends from withdrawn

claim 26, claim 30 depends from withdrawn claim 36, and claims 57 and 58 depend from withdrawn claim 54. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7, 28-32, 35 and 56-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1-4, 28-32 and 56-58 require the use of "an agent that activates the growth pathway of CNS neurons." A few examples of such agents are described at pp.23-25 of the specification and can include "any agent" that has the described functional activity. Similarly, claims 1-4, 7, 31, 32 and 35 require the use of "an NgR antagonist." A few examples of such antagonists are described at paragraphs [0011], [0039]-[0046], and [0067]-[0068] and can include "any agent capable of suppressing the activity of the Nogo receptor." However, these portions of the specification do not describe the structure, which amino acid residues or nucleic acid residues are present, for example, in the genus of agents that activate the growth pathway of CNS neurons or

in the genus of NgR antagonists. Although the specification provides a few examples of members of each genus, it fails to disclose the structures common to all members of the genus encompassed by the broad definition provided by applicants. The specification does not disclose the structure of all variant molecules encompassed by "an agent that activates the growth pathway of CNS neurons" and does not disclose which regions of the agents are responsible for activating the growth pathway of CNS neurons, which is stated to be common to all members of the genus. Applicants are directed to the recently-published guidelines on interpretation of the written description requirement, available on the internet at: http://www.uspto.gov/web/menu/written.pdf . See in particular Examples 9 and 10, drawn to protein variants including those with recited functions. Since the specification does not disclose which the structures common to all agents that activate the growth pathway of CNS neurons and does not disclose which structures are either necessary or sufficient such that members of the genus have the required activity, the claims do not meet the written description requirement.

With regards to NgR antagonists, applicants have not described a reasonable number of members of the genus now claimed, but rather has presented the public with an idea of how to perform an assay that might identify some agents that fall within the scope of the claim (see paragraph 0067, which clearly states that antagonists can be identified by screening assays). Of course, depending on what agents are used in the screening assay, it may well identify none. The instant claims are often referred to as "reach-through" claims, where an applicant attempts to obtain patent protection on an invention not yet discovered. The Court of Appeals for the Federal Circuit addressed

claims of this sort in great detail in *University of Rochester v. G.D. Searle and Co.* (69 USPQ 2nd 1886, CAFC 2004). In *Rochester*, the Federal Circuit upheld the district court's ruling that patent claims which recited administration of compounds not disclosed, but rather to be identified in a screening assay, were invalid on their face. Since the specification does not disclose to the public the structures used as starting materials in the presently-claimed methods, it does not meet the written description requirement of 35 USC § 112, first paragraph.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 is dependent on nonelected claim 36, but recites the limitation "wherein said viral vector is AAV," which implies that the claim should be dependent on claim 29. Furthermore, non-elected claim 36 does not recite a viral vector. Therefore, claim 30 is open to multiple interpretations and thus, the metes and bounds of the claim cannot be ascertained. Appropriate correction is required.

It is noted that, for the purposes of applying prior art, claim 30 will be interpreted as dependent on claim 29.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 7, 31, 32 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Schwab et al. (WO 94/17831, published 18 August 1994; Cited on IDS dated 14 March 2008) as evidenced by Chen et al. (Nature 2000, Cited on IDS dated 14 March 2008).

Schwab et al. teach methods of promoting CNS axonal regeneration in a mammalian subject in need thereof (e.g. in subjects after SCI) comprising administering a therapeutically effective amount of an essentially purified and isolated neurotrophin family member (e.g. NT-3, BDNF or NGF), together with an antibody directed toward a myelin-associated neurite growth inhibitory protein (see paragraph spanning pp.3-4). The antibody is interpreted as meeting the claimed limitation of an NgR antagonist, as evidenced by Chen et al. Chen et al. (which has includes both of the inventors of the Schwab WO document) describe the cloning of Nogo and provides evidence that the antibodies against the myelin-associated neurite growth inhibitory protein of the WO document are in fact antibodies against Nogo. It is noted that the instant specification

defines an NgR antagonist to include agents that bind to Nogo, including antibodies (see paragraph 0011). Therefore, Schwab et al. (the WO document) teaches all the limitations of claims 1, 2, 7, 31, 32 and 35.

Claims 1, 2, 31 and 32 are rejected under 35 U.S.C. 102(e) as being anticipated by Strittmatter et al. (US 2003/0124704 A1, published 03 July 2003, earliest priority date of 06 October 2000; Citation A on PTO-892 dated 11 June 2009).

Strittmatter et al. teach methods and compositions for stimulating the axonal growth of central nervous system (CNS) neurons (e.g. in a method of treating a neurological disorder) comprising administration to mammals, e.g. humans, of therapeutically effective amounts of an NgR antagonist and a growth factor (see e.g. paragraphs 0001-0009, 0017, 0018, 0195 and 0196), thus meeting the limitations of claims 1, 2 and 31. Strittmatter et al. teach that the neurological disorder to be treated can be cerebral injury, spinal cord injury (SCI), stroke, and demyelinating diseases, e.g., multiple sclerosis, monophasic demyelination, encephalomyelitis, and multifocal leucoencephalopathy (0018), thus meeting the limitations of claim 32.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 7, 28-32, 35 and 56-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwab et al. (WO 94/17831, published 18 August 1994; Cited on IDS dated 14 March 2008) as evidenced by Chen et al. (Nature 2000, Cited on IDS dated 14 March 2008), and further in view of Dergham et al. (Rho signaling pathway targeted to promote spinal cord repair. J Neurosci. 2002 Aug 1;22(15):6570-7).

As set forth above, Schwab et al. teach methods of promoting CNS axonal regeneration in a subject in need thereof (e.g. in subjects after SCI) comprising administering a therapeutically effective amount of an essentially purified and isolated

neurotrophin family member (e.g. NT-3, BDNF or NGF), together with an antibody directed toward a myelin-associated neurite growth inhibitory protein (see paragraph spanning pp.3-4), as in claims 1, 2, 7, 31, 32 and 35. The antibody is interpreted as meeting the claimed limitation of an NgR antagonist, as evidenced by Chen et al. Chen et al. (which includes both of the inventors of the Schwab WO document) describe the cloning of Nogo and provides evidence that the antibodies against the myelin-associated neurite growth inhibitory protein of the WO document are in fact antibodies against Nogo. It is noted that the instant specification defines an NgR antagonist to include agents that bind to Nogo, including antibodies (see paragraph 0011). Therefore, Schwab et al. (the WO document) teaches the required limitations of claims 1, 2, 7, 31, 32 and 35. The difference between the claimed invention and that of Schwab et al. is that the latter do not teach administration of the specifically elected NgR antagonist of botulinum C3 ADP-ribosyltransferase (C3).

However, Dergham et al. teach treatment of spinal cord injured mice comprising administration of an effective amount of the claimed C3, which was sufficient to stimulate axon regeneration and recovery of hindlimb function after spinal cord injury (SCI; see e.g. abstract), as in claims 28-30 and 56-58. Dergham et al. states that C3 blocks Rho protein function, which results in neurite outgrowth in the presence of myelin (p.6570, paragraph 3). Dergham et al. also suggests that axonal growth can be stimulated in adult CNS neurons after injury with neurotrophins, which are known to delay apoptosis, prevent atrophy of axotomized neurons, and enhance the expression of growth-associated genes (p.6570, paragraph 2). It is noted that the limitations of

claims 28-30 and 56-58, i.e. "encoded by DNA," "wherein said DNA is contained in a viral vector whereby administration of said vector is a means for contacting CNS neurons with an effective amount of NgR antagonist," and "wherein said viral vector is AAV" are not active method steps. Rather, these are "product-by-process" limitations. Thus, the patentability of the method claims which recite administration of the product is based on the method of administering the product itself (i.e. botulinum C3 ADP-ribosyltransferase) and does not depend on its method of isolation of the starting material (see MPEP §2113). Since Dergham et al. teach administration of C3, they describe this active administration step in claims 28-30 and 56-58. Applicants bear the burden of establishing a patentable distinction between the claimed C3 and the prior art C3 of Dergham et al. The difference between the claimed invention and that of Dergham et al. is that the latter do not teach administration of the additional active agent that activates the growth pathway of CNS neurons, as claimed.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed to combine the teachings of Schwab et al., Chen et al. and Dergham et al. to arrive at the combination therapy comprising methods of using botulinum C3 ADP-ribosyltransferase and a neurotrophin family member for promoting axonal growth of CNS neurons, as claimed. As recognized in the Schwab reference, co-administration of a neurotrophin family member together with an antibody directed toward a myelin-associated neurite growth inhibitory protein would be effective to treat spinal cord injury by inducing axonal growth. As recognized in the Dergham reference, administration of C3, which is another inhibitor of a myelin-associated neurite growth

inhibitory protein, would be effective to treat spinal cord injury by inducing axonal growth. Thus, one of skill in the art would have been motivated to substitute Dergham's botulinum C3 ADP-ribosyltransferase in place of Schwab's antibody and would have had a reasonable expectation that the administered combination of agents, i.e. C3 administered with the neurotrophin family member would be beneficial for the treatment of the disease. The artisan would have been further motivated to administer neurotrophins along with C3 based on Dergham's explicit teaching that neurotrophins also stimulate axonal growth in the CNS and since Chen et al. provides motivation to swap anti-Nogo antibodies with other known inhibitors (such as those from Dergham). As in stated in MPEP §2144.06, substituting one equivalent element for another known for the same purpose renders an invention obvious and an "express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)." Moreover, this section of the MPEP teaches "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose .... [T]he idea of combining them flows logically from their having been individually taught in the prior art. *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted). Accordingly, the cumulative reference teachings render the claimed method obvious.

Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwab et al. (WO 94/17831) as evidenced by Chen et al., in view of Dergham et al. (J Neurosci. 2002) as applied to claims 1, 2, 7, 28-32, 35 and 56-58 above, and further in view of Neumann et al. (Regeneration of sensory axons within the injured spinal cord induced by intraganglionic cAMP elevation. Neuron 2002, June 13; 34(6): 885–893).

The relevant disclosures of Schwab et al., Chen et al. and Dergham et al. are set forth above. It is noted that the Dergham reference additionally teaches that neurotrophins might stimulate regeneration by increasing neuronal cAMP levels to overcome inhibitory signaling (p.6570, paragraph 2). Thus, Dergham provides evidence that the neurotrophin treatment of Schwab is on point to claim 3, i.e. that the neurotrophin is a cAMP modulator that increases the concentration of intracellular cAMP. Therefore, the combination of Schwab and Dergham may be sufficient to meet the limitations of claim 3, in that these references suggest that neurotrophins are both agents that activate the growth pathway of CNS neurons (as recited by independent claim 1) and are cAMP modulators that increase the concentration of intracellular cAMP (as recited by dependent claim 3). However, claim 3 recites "further comprising contacting CNS neurons with a cAMP modulator that increases the concentration of intracellular cAMP" suggesting that claims 3 and 4 comprise administration of three separate agents. Accordingly, Neumann et al. teach that administration of a membrane-permeable cAMP analogue markedly increases CNS axonal regeneration after SCI (see e.g., abstract), as in claims 3 and 4.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed to combine the teachings of Schwab et al., Chen et al., Dergham et al. and Neumann et al. to arrive at the combination therapy comprising methods of administering C3, a neurotrophin and a cAMP analog for promoting axonal growth of CNS neurons, as claimed. As recognized in the Schwab reference, co-administration of a neurotrophin family member together with an antibody directed toward a myelin-associated neurite growth inhibitory protein (an antibody against Nogo, as evidenced by Chen et al.) would be effective to treat spinal cord injury by inducing axonal growth. As recognized in the Dergham reference, administration of C3, which is another inhibitor of a myelin-associated neurite growth inhibitory protein, would be effective to treat spinal cord injury by inducing axonal growth. As recognized in the Neumann reference, administration of cAMP analogues would be effective to treat spinal cord injury by inducing axonal growth. Thus, one of skill in the art would have been motivated to substitute Dergham's botulinum C3 ADP-ribosyltransferase in place of Schwab's antibody and administer cAMP analogues as taught by Neumann and would have a reasonable expectation that the administered combination of agents, i.e. C3, neurotrophin and cAMP analogue, would be beneficial for the treatment of the disease. As in stated in MPEP §2144.06, substituting one equivalent element for another known for the same purpose renders an invention obvious and an "express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)." Moreover, this section of the MPEP teaches "It is *prima facie* obvious to

combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose .... [T]he idea of combining them flows logically from their having been individually taught in the prior art. *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted). Accordingly, the cumulative reference teachings render the claimed method obvious.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Peel et al. (Adeno-associated virus vectors: activity and applications in the CNS. J Neurosci Methods. 2000 Jun 1;98(2):95-104) teach the desirability of using adeno-associated vectors (AAV) for CNS gene therapy treatment methods and discloses that BDNF gene transfer was effective in treating spinal cord injury (see p.101).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone

number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G.E./

Gregory S. Emch
Patent Examiner
Art Unit 1649
22 November 2009

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
November 23, 2009